Institution: University of Leicester

Unit of Assessment: 1

Title of case study: CvLPRIT: Changing Global Clinical Practice for Patients Presenting with ST Elevation Myocardial Infarction Heart Attack

Period when the underpinning research was undertaken: 01/01/2010 – 31/12/2014

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
1. Professor Anthony Gershlick 2. Professor Gerry McCann	1. Professor of Cardiology 2. Professor of Cardiac Imaging and Honorary Consultant Cardiologist	1. 2005 – November 2020 2. 2014 – Present

Period when the claimed impact occurred: 2014 – 2019

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact

Prior to the multicentre CvLPRIT (Complete versus Lesion-only PRImary PCI Trial) study, International guidelines recommended that patients presenting with ST elevation myocardial infarction (STEMI) and multivessel disease should only have the blocked artery treated, as treatment of narrowing in other arteries was considered harmful. The randomised CvLPRIT study significantly helped reverse this recommendation by demonstrating clinical benefit when both the blocked and bystander narrowings were treated. The trial helped change global clinical practice with complete revascularisation recommended in the EU and US guidelines for the management of STEMI, and the UK NICE Guidelines for Acute Coronary Syndromes.

2. Underpinning research

STEMI is caused by a sudden and complete obstruction of a coronary artery, which is also known as the infarct related artery (IRA). Primary Percutaneous Coronary Intervention (PPCI) improves outcomes, including mortality, by reliably restoring blood flow and limiting myocardial damage. It is performed as an emergency in a cardiac catheter laboratory using wires, balloons and stents under x-ray guidance. In up to 50% of STEMI patients, at least one other coronary artery—the so-called non-infarct related artery (N-IRA)—is also noted to have a narrowing. The American Heart Association/American College of Cardiology Guidelines (AHA/ACC), published in 2013, recommended that the N-IRA should **not** be treated, primarily based on registry data. However, registry data are very prone to bias and observed results may not be reliable.

Gershlick and colleagues designed the first clinically robust randomised trial, funded by the British Heart Foundation **[G1]**, comparing complete revascularisation (treatment of the N-IRA in addition to treatment of the IRA), with treatment of the IRA alone. CvLPRIT **[R1]** was led by Professor Gershlick, the chief investigator, and recruited 296 patients in seven UK centres. The CvLPRIT Cardiac MRI sub-study was led by Professor McCann **[R2, R3]** through a grant from MRC/NIHR EME [**G2]** and recruited 203 of 296 patients in the main study. A cost efficacy analysis was conducted in collaboration with the University of East Anglia **[R4]**, and a Myocardial Perfusion Nuclear sub-study was co-ordinated through collaboration with the Royal Brompton Hospital **[R5]**.

The first patient was recruited at University Hospitals of Leicester in May 2011 and the last in May 2013, with the final 12-month follow up performed in May 2014. The trial was published in

2015. It concluded that in STEMI patients, complete revascularisation resulted in a significant reduction in composite major adverse cardiovascular events (MACE; death, further heart attack, heart failure, or need for repeat revascularization). This primary MACE endpoint occurred in 10.0% of those randomised to complete revascularisation compared to 21.2% in the IRA-only revascularisation group (hazard ratio: 0.45; 95% confidence interval: 0.24-0.84; p=0.009). The trend toward benefit was seen early after complete revascularisation (p=0.055 at 30 days) **[R1]**. Although there was no significant reduction in death or myocardial infarction alone at 12 months, a significant reduction in these hard endpoints (10.0% vs 18.5%; hazard ratio: 0.47; 95% confidence interval: 0.25 to 0.89; p=0.0175) has been shown in the CvLPRIT long–term follow-up study, which assessed outcomes up to a median of 5.6 years **[R6]**.

Another randomised trial (the PRAMI trial), presented shortly before CvLPRIT, was criticized for various aspects of its design and was consequently deemed unreliable. Therefore, while CvLPRIT was the second trial in the field, it was the first to successfully demonstrate benefit with appropriate rigour, and applicability to cardiology patients worldwide. CvLPRIT results initiated a review of their recommendations by the AHA/ACC Guideline Committee. The findings from CvLPRIT have been substantiated by three further trials (DANAMI-3-PRIMULTI, COMPARE-ACUTE and COMPLETE) and a subsequent meta-analysis has confirmed a reduction in cardiovascular mortality (OR, 0.69 [95% CI, 0.48-0.99], p=0.05) and the combined endpoint of cardiovascular death or MI (OR, 0.69 [95% CI, 0.55-0.87]; P = 0.001) with complete revascularisation **[R7].**

3. References to the research

R1. Gershlick AH, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, …..**McCann GP**. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol. 2015;65(10):963-72.

R2. McCann GP, Khan JN, Greenwood JP, Nazir S, Dalby M, Curzen N,….**Gershlick AH**. Complete Versus Lesion-Only Primary PCI: The Randomized Cardiovascular MR CvLPRIT Substudy. J Am Coll Cardiol. 2015;66(24):2713-24.

R3. Khan JN, Nazir SA, Greenwood JP, Dalby M, **Gershlick AH**, **McCann GP**. Infarct size following complete revascularization in patients presenting with STEMI: a comparison of immediate and staged in-hospital non-infarct related artery PCI subgroups in the CvLPRIT study. J Cardiovasc Magn Reson. 2016;18(1):85.

R4. Barton GR, Irvine L, Flather M, **McCann GP**, Curzen N, **Gershlick AH**, et al. Economic Evaluation of Complete Revascularization for Patients with Multivessel Disease Undergoing Primary Percutaneous Coronary Intervention. Value Health. 2017;20(6):745-51.

R5. Kelion AD, Pakkal MV, Chowdhury FU, Birchall JD, **McCann GP**, **Gershlick AH**. Ischemia and Infarction in STEMI Patients With Multivessel Disease: Insights From the CvLPRIT Nuclear Substudy. J Am Coll Cardiol. 2016;67(22):2698-9.

R6. Gershlick AH, Banning AS, Parker E, Wang D, Budgeon CA, Kelly DJ, … **McCann GP** et al. Long-Term Follow-Up of Complete Versus Lesion-Only Revascularization in STEMI and Multivessel Disease: The CvLPRIT Trial. J Am Coll Cardiol. 2019;74(25):3083-94.

R7. Bainey KR, Engstrøm T, Smits PC, **Gershlick AH**, James SK, Storey RF, Wood DA, Mehran R, Cairns JA and Mehta SR, et al. Complete vs Culprit-Lesion-Only Revascularization for ST-Segment Elevation Myocardial Infarction: A Systematic Review and Meta-analysis. *JAMA Cardiology.* 2020;5(8):881-888.

Grants

G1. Complete **v**ersus **L**esion only **PRI**mary PCI Pilo**T** (**CvLPRIT**). Professor A H Gershlick. British Heart Foundation. GBP366,600 (01/01/2010 – 31/12/2014).

G2. Complete **v**ersus **L**esion only **PRI**mary PCI Pilo**T** (**CvLPRIT**) CMR substudy. Professor G P McCann. MRC/National Institute of Health Research Efficacy and Mechanism Evaluation. GBP384,899 (01/04/2011 – 31/12/2013).

4. Details of the impact

Prior to CvLPRIT, patients who presented with STEMI heart attack and multi-vessel disease would normally have only the blocked coronary artery (or IRA) opened. The results of the CvLPRIT study altered the way clinicians considered how such patients should be managed. More importantly, it was central in changing impactful Clinical Guidelines, influencing patient care and improving health outcomes globally.

The time sequence of events and research citations in revised clinical practice guidelines clearly demonstrate the impact of CvLPRIT and how it has changed clinical practice in the UK, Europe and the US.

Professor Gershlick presented the CvLPRIT results at the European Society of Cardiology (ESC) Congress in 2014 to an audience of 3000 attendees and a moderator panel of international experts, which included the Chair of the AHA/ACC Guidelines Committee **[E1].** Following this presentation, and the subsequent publication of the results in 2015, focussed updates to clinical guidelines were made based on this trial, by both the AHA/ACC (2015) **[E2]** and European Society of Cardiology (ESC 2016) Guideline Committees, which for the first time recommended to physicians to consider treatment of the bystander (N-IRA) disease **[E3].** Prior to CvLPRIT this practice was not recommended—indeed, it was actively discouraged—but following the presentation, publication and full data review, the Guidelines were updated and now recommend that a new approach be considered for the management of STEMI patients with N-IRA disease. As well as the AHA/ACC and ESC Guideline recommendations, the recently published NICE Guidelines for Acute Coronary Syndromes **[E4]** also recommend complete treatment of IRA and N-IRA as per the results of the CvLPRIT study. NICE guidance takes into consideration cost-effectiveness and highlights the lower cost associated with complete revascularisation seen in CvLPRIT **[E4, R4].**

Subsequent randomised studies supported the findings shown in CvLPRIT. Thus, by 2017, two additional randomised trials had been published supporting the treatment of the N-IRA in addition to the IRA. One difference between these trials was the timing of the intervention on the N-IRA. Only CvLPRIT provided clarity on when this was undertaken, with all patients receiving treatment of the N-IRA prior to discharge. This influenced the latest 2017 ESC STEMI Guidelines **[E3]** which went further with its recommendation (IIa A) that complete revascularisation should be performed "before hospital discharge", as per the CvLPRIT protocol. In 2020, Professor Stefan James, who chaired the ESC Clinical Guidelines Committee confirmed that: ***"the trial directly influenced the ESC Guidelines recommendations on treating patients with ST elevation MI undergoing primary PCI. These guidelines were well respected which made a significant impact on clinical practice"*** **[E5]**.

In 2020, the NICE 'Acute Coronary Syndromes' guideline was updated to recommend complete revascularisation with PCI for patients with acute STEMI and multivessel coronary artery disease without cardiogenic shock. This change was made following extensive evidence review in which CvLPRIT was highly influential as the first study assessing patients with myocardial infarction and ST elevation scheduled for primary PCI which demonstrated and recommended treatment

of the IRA first followed by complete revascularisation during the index admission; a crucial reason for the guideline change **[E4]**.

Clinical Impact

UK British Heart Foundation statistics indicate that mortality from coronary artery disease in 2017 was approximately 65,000. In the same year, World Health Organisation figures estimated 17.9 million people died from cardiovascular disease annually, representing 31% of all global deaths. Of these, 85% are due to heart attack and stroke. Since up to 50% of patients who present with STEMI heart attack have multi-vessel disease, a significant number of patients stand to benefit if the revised, and now evidenced-based, guideline-directed management strategies are adopted in everyday clinical practice. In 2020, UK STEMI incidence was between 750 and 1250 cases per million people: between 50,250 and 83,750 cases requiring hospitalisation **[E4].** Given the 3% reduction in cardiovascular death or MI demonstrated by the meta-analysis **[R7]**, a minimum of 1,500 deaths or heart attacks would be prevented per year in the UK alone. In the USA, this figure is up to ~11,500 **[E6].** As the population of Europe is double that of the US, these changes in management strategy will also provide significant clinical impacts across Europe and the rest of the world.

Guideline committees now support multi-vessel intervention **[E2, E3, E4]** as a result of CvLPRIT. Clinicians must therefore make a proactive decision to treat the N-IRA, rather than depending on the development of symptoms during clinical follow-up as they may have done previously.

In 2019, to ascertain the effect of CvLPRIT on clinical practice, Professor Gershlick undertook a global survey of interventional cardiologists using the International Cardiovascular Research Foundation **[E7].** The majority of respondents indicated that their clinical practice relating to STEMI had changed since 2014 with most citing published clinical trials as their reason. When asked to name the trials that most influenced the changes, CvLPRIT was the most cited study and highlighted in 46% of responses to this question, with the other three trials making up the rest. Although the respondents were self-selecting and, therefore, not necessarily representative of all clinicians, the snapshot the survey indicates that CvLPRIT, above all other randomised studies at the time, has significantly influenced clinical practice through its publication and impact on international guidelines. These data are supported by a large, nationwide analysis of US practice (>350,000 patients) that has demonstrated that rates of multi-vessel PCI use in patients with STEMI have steadily increased from a nadir of 32.7% in 2013, to a peak of 44.0% of cases in 2017 (following publication of the ACC/AHA guidelines) **[E8].** Importantly, during this time, multi-vessel PCI was most commonly undertaken during the index procedure or hospital admission (69.2%), again as per the protocol used in CvLPRIT.

CvLPRIT has also stimulated and driven further scientific enquiry. It has led to the initiation and conduct of three large international trials, designed to answer some subsidiary but important questions raised by CvLPRIT findings. The combined MACE endpoint in CvLPRIT included repeat revascularisation – the subsequent COMPLETE trial reported hard endpoints only (death and further heart attack) and was presented at the ESC Congress 2019 and subsequently published in the *New England Journal of Medicine* **[E9]**. COMPLETE had sufficient power to demonstrate a reduced risk of death or further heart attack when complete revascularisation was performed. It essentially validated the findings of CvLPRIT and the CvLPRIT long-term follow-up study, in a larger patient population. Professor Shamir Mehta, Professor of Medicine at McMaster University and Director of the Interventional Cardiology program at Hamilton Health Sciences, Canada and the COMPLETE Trial Chief Investigator confirmed that ***"CvLPRIT … has had an important impact on clinical practice and in shaping the Guidelines on both sides of the Atlantic"*** **[E10]**. Two further studies have been initiated: one, FLOWER-MI

(ClinicalTrials.gov Identifier: NCT02943954) is in recruitment phase and FULL REVASC (ClinicalTrials.gov Identifier: NCT02862119) (which has ceased recruitment since COMPLETE has been published) set out to investigate how to best select which N-IRA required treatment with PCI using invasive coronary artery physiology assessment. The PI of the FULL REVASC trial has stated that CvLPRIT *"was of great importance for the design"* of the trial **[E11].** The FIRE trial (ClinicalTrials.gov Identifier NCT03772743) will be assessing complete revascularisation in the elderly and quotes CvLPRIT as its reference point, along with the other studies.

The recently published CvLPRIT long-term follow-up data have provoked further focus in the cardiovascular community on multi-vessel intervention in STEMI, and provided further data to support the reduction in hard clinical endpoints from multi-vessel intervention seen in the COMPLETE study **[R6, R7, E10, E12].**

In summary, CvLPRIT has informed international Clinical Practice Guidelines, changed contemporary clinical practice, improved patient health outcomes and defined future research direction within the field.

5. Sources to corroborate the impact

E1. ESC Congress 2014 press release: https://www.tctmd.com/news/cvlprit-complete-revascularization-halves-mace-risk-stemi-patients

E2: AHA/ACC 2015 Focussed Update of STEMI Guidelines: https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000336

E3. ESC 2017 STEMI Guidelines: https://academic.oup.com/eurheartj/article/39/2/119/4095042

E4. NICE Draft Guideline 'Acute Coronary Syndromes' February 2020 (See also Evidence Reviews D,E and F): https://www.nice.org.uk/guidance/GID-NG10085/documents/short-version-of-draft-guideline

E5. Testimonial: Senior Consultant Cardiologist, Upsala University Hospital, Sweden.

E6. Akbar, H et al. 'Acute Myocardial Infarction ST Elevation (STEMI), StatPearls, Jan 2020. https://www.ncbi.nlm.nih.gov/books/NBK532281/

E7. Multi-vessel Intervention in STEMI global questionnaire results.

E8. Secemsky et al, "Temporal Changes and Institutional Variation in Use of Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction With Multivessel Coronary Artery Disease in the United States", *JAMA Cardiology*. https://jamanetwork.com/journals/jamacardiology/article-abstract/2772315

E9. COMPLETE Trial: https://www.nejm.org/doi/full/10.1056/NEJMoa1907775

E10. Testimonial: Professor, Department of Medicine, McMaster University, Hamilton General Hospital, USA.

E11. Testimonial: Consultant Interventional Cardiologist, Karolinska Institute, Sweden.

E12. TCT 2018 press release: https://www.tctmd.com/news/cvlprit-long-term-reduction-deathmi-complete-revascularization